IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Keiichi FUJIWARA et al.
Appln. No.: 10/582,174 Group Art Unit: 1612
Filed: December 7, 2004 Examiner: GIGI HUANG
For: DRUG-CONTAINING GRAINS AND SOLID PREPARATION CONTAINING THE GRAINS

DECLARATION

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

I, Norihito SHIMONO, a citizen of Japan and residing at No. 3-13, Ibukidainishi-machi 6-chome, Nishi-ku, Kobe-shi, Hyogo, Japan, declare and say as follows.

1. I was graduated from the Kyoto University, Faculty of Pharmacy, Department of Pharmaceutical Sciences, Japan in March 1986, and completed the master's course at the same university, Graduated School of Pharmaceutical Sciences in March 1988, and awarded the degree of Doctor of PH from the Kyoto University, Graduated School of Pharmaceutical Sciences in January 2003.

2. Since April 1988 up till the present, I have been an employee of Dainippon Sumitomo Pharma Company, Limited (former Dainippon Pharmaceutical Company, Limited), and I have been engaged in research work of pharmaceutical formulations for 22 years and now I am handling development management work of Technology Research & Development Division in Medical Product Research Laboratory of said company.

3. I am one of the inventors of the present U.S. Patent Application No. 10/582,174 and am familiar with the present invention.

4. Based upon my knowledge and experience in the drug formulation

fields, I can say as follows.

5. In order to prove that the medicament-containing particle of the present invention lacks for a coating, I and co-researchers have carried out the following additional experiment; i.e. a medicament-containing particle of the present invention was prepared and the surface of the particle was examined by means of a Laser Raman microspectroscope.

6. A medicament-containing particle was prepared based on the composition shown in the following Table 1 (each ingredient in Table 1 is the same materials described in the present specification). That is, mannitol and methylcellulose were added to a fluid bed granulator (Powrex Corp., GPCG-120) and mixed and then a suspension of 4% HPC-L water-solution and mosapride citrate dihydrate (as a medicament) was spray-added to the fluid bed granulator in which the content was mixed and granulated. Then, the resulting granules were dried in the bed. (Please note that the above-mentioned process is a little modified from the process described in the present specification because of its scale-up, but I believe that the essence of the both particles is identical.)

Table 1

Ingredient	Amount
Mosapride citrate	21.16 kg (21.16 %)
D-mannitol	56.84 kg (56.84 %)
Methylcellulose	20 kg (20.00 %)
Hydroxypropylcellulose (HPC-L)	2 kg (2.00 %)

7. Using the resulting medicament-containing particle, the surface thereof was examined by means of a Laser Raman microspectroscope. The condition of a Laser Raman microspectroscope is as follows.

Laser Raman microspectroscope: LabRAM ARAMIS (HORIBA, Ltd., Japan)

Wave Length: 633 nm

Grating: 300

Magnification: x 20

[Laser Raman microspectroscopy makes it possible to identify each material included on the surface of the particle by means of Laser irradiation. Namely, every material has its inherent Raman signal peak based on the scattered light produced by irradiating Laser on the material.

And, it is possible to assign the peak value to a specific color. Using the mechanism, it is possible to identify what ingredients are included on the surface through specified colors.]

8. First of all, the photographic images of each ingredient's surface are shown in the attached Figures 1-4. In Figure 1 mosapride citrate is shown in orange-red. In Figure 2, D-mannitol is shown in green. In Figure 3, methycellulose is shown in purple. In Figure 4, HPC-L is shown in dark-blue. Each right image is obtained by expanding the square drawn in the left image.

9. Next, a composite photographic image of the medicament-containing particle prepared as above which combines the colorations from Figures 1-4 is shown in the attached Figure 5. The image on the right was obtained by expanding the square drawn in the left image.

10. According to the photographic image of the medicament-containing particle shown in Figure 5, the surface of the particle includes various colors, i.e. the images show that each ingredient is homogeneously dispersed in the surface. In particular the medicament (mosapride citrate), indicated as orange-red color, is present on the surface of the particle. Accordingly the photographs establish that the medicament with an unpleasant taste is located in the surface without coating.

11. Furthermore, in order to make clear that the particle is uncoated, the medicament-containing particle of the present invention was observed with an Electron Microscope. The sample for being observed with an Electron Microscope was prepared according to the process described in the above paragraph 6, provided that the preparation scale was scaled down as shown in Table 2.

Table 2

Ingredient	Amount
Mosapride citrate	7.935 kg (21.16 %)
D-mannitol	21.315 kg (56.84 %)
Methylcellulose	7.5 kg (20.00 %)
Hydroxypropylcellulose (HPC-L)	0.75 kg (2.00 %)

12. The Electron Microscope used in this experiment was Scanning

Electron Microscope S-3400N (Hitachi High-Technologies Corporation, Japan). The result is shown in the attached Figure 6 (the left image is a 100-fold image and the right one is a 500-fold image). Each of the structures is an individual particle, as shown by the scale at the bottom of the images. As is evident from the electron microscopical image, the surfaces of the particles are scabrous. This type of structure indicates that the particles are not coated. If the particles had been coated, the surfaces would be more smooth and the particles would be in a spherical or subspherical form. Thus, the result proves that the presently claimed particle is not coated.

13. In conclusion, it is definite that the particles of the present invention are uncoated and the ingredients are homogeneously dispersed in the particle, from the above experiments.

14. It is my opinion, based upon my knowledge and experience in this field, the particle of the present invention has a very excellent masking effect though a medicament with an unpleasant taste is located on the surface of the particle and also the particle is uncoated. Such a result would be unexpected to one of skill in the art, especially since one of skill in the art would expect that direct contact between an individual's tongue and the medicament having an unpleasant taste would cause an unpleasant taste to be felt by the individual. I believe that the present invention which enables a masking of unpleasant taste even though a medicament with an unpleasant taste is located on the surface of the particle is a very excellent particle. Moreover, the taste-masking effect would not be expected in view of the structure of the claimed particles, especially in view of the teachings in the art that coating is required to mask the taste of unpleasant tasting drugs.

15. The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the above-identified application or any patent issuing thereon.

This 4th day of November, 2010

Norihito Shimono

Norihito SHIMONO, Ph.D.

Attached Document to the Dr. Shimono's Declaration:

Figures 1-6

Figure 1. Photographic image of mosapride citrate by means of Laser Raman microspectroscope.

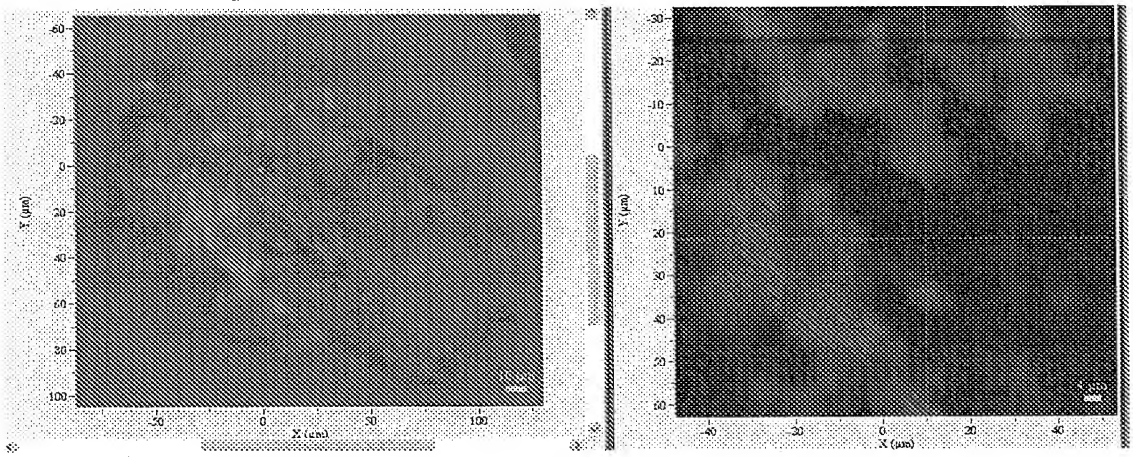

Figure 2. Photographic image of D-mannitol by means of Laser Raman microspectroscope.

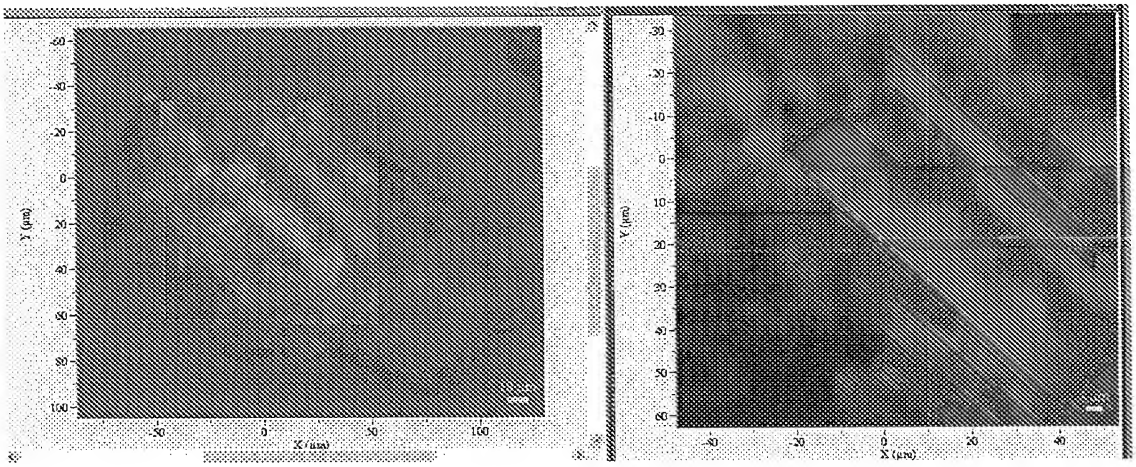

Figure 3. Photographic image of methylcellulose by means of Laser Raman microspectroscope.

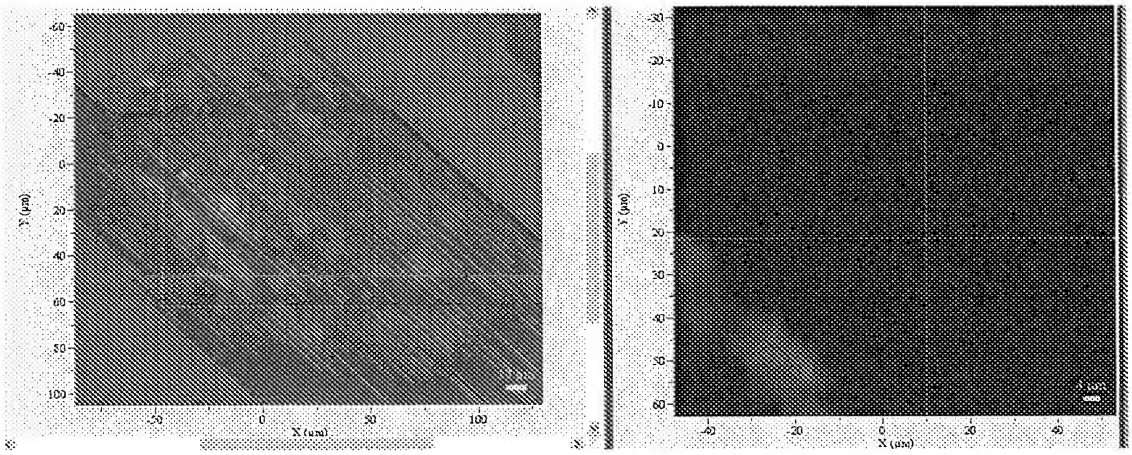

Figure 4. Photographic image of HPC-L by means of Laser Raman microspectroscope.

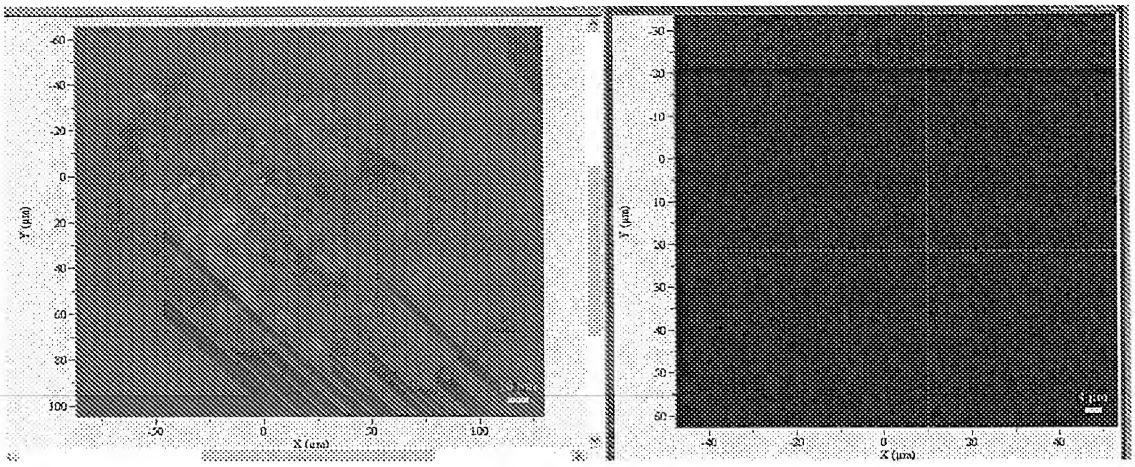

Figure 5. Photographic image of medicament-containing particle by means of Laser Raman microspectroscope.

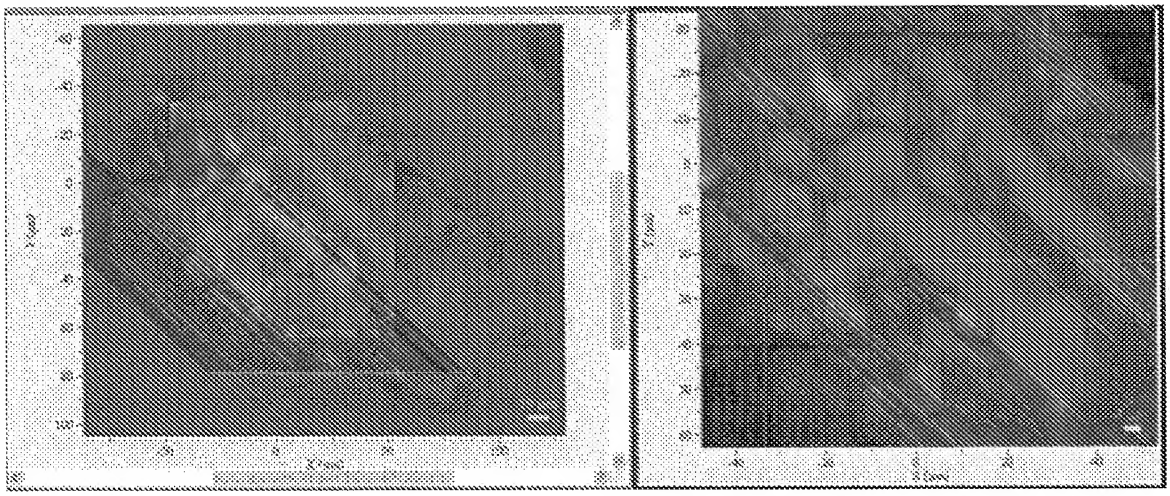

Figure 6. Electron microscopical image medicament-containing particle by means of Electron Microscope.